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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,950	05/10/2007	Wesley Blackaby	21573YP	5436

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

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07/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,950	BLACKABY ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,18-20 and 22-27* is/are pending in the application.

4a) Of the above claim(s) *9,20 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-14,18,19,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/23/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

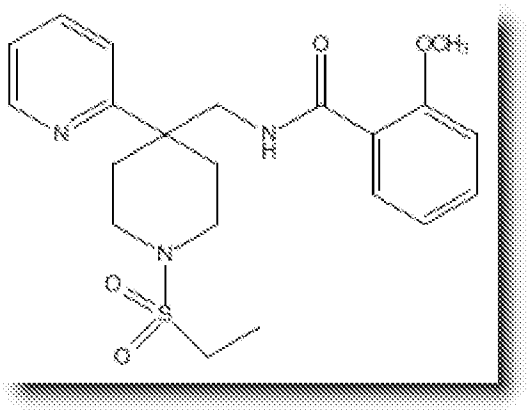
Status of the Claims

1. The amendments filed 03/23/2009 were entered.

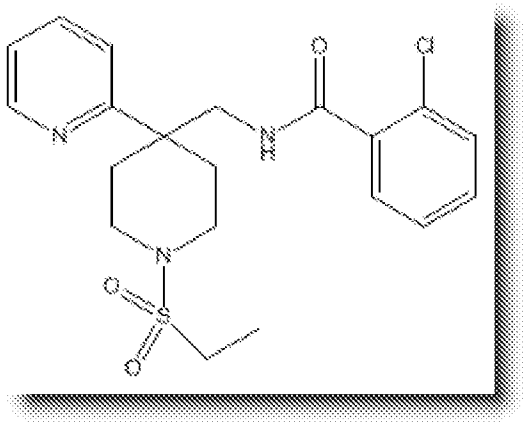
Response to Arguments

2. Applicants' arguments, filed 03/23/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. In particular, the rejection of claims under 35 USC § 103 as being unpatentable over *Bao et al* as evidenced by *Rogers et al* in view of *Williams et al* and *Patani et al* is withdrawn in view of Applicants' amendments to the claims. As such, Applicants' arguments as to this rejection have been rendered moot. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Election/Restrictions

3. As discussed in the previous Action, since the elected species was searched and is deemed free of the prior art, the search was therefore expanded as called for under current Office Markush Practice - a compound by compound search - to include a single additional species. That compound species was  . However, by

amendment, Applicants have overcome the rejection based on the above compound species. Accordingly, the search was therefore expanded again as called for under current Office Markush Practice - a compound by compound search - to include a single additional species.

That species is  wherein R^1 is hydrogen; R^2 is phenyl, which is substituted with R^{2a} and R^{2a} is halogen; R^3 is CH_2-CH_3; R^4, R^5 and R^6 are hydrogen; W, X, Y and Z are C; and m is zero, which reads on claims 1-4 and 10-14. A rejection as to those claims follows.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

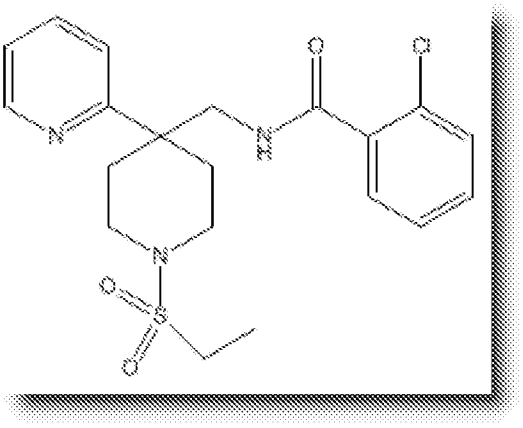
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

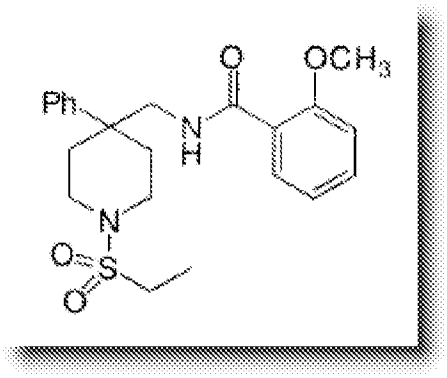
5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 1-4, 10-14, 18-19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Bao et al* (cited in a previous Action) in view of *Williams et al* (cited in a previous Action) and *Patani et al* (cited in a previous Action)**.

7. The following rejection is necessitated by Applicants' amendments to the claims.

8. Instant claim 1, as amended, is drawn to a compound of formula (I) which encompasses the following compound species  wherein R^1 is hydrogen; R^2 is phenyl, which is substituted with R^{2a} and R^{2a} is halogen; R^3 is CH_2-CH_3; R^4, R^5 and R^6 are hydrogen; W, X, Y and Z are C; and m is zero, which reads on claims 1-4, 11-14 and 18-19.

9. *Bao et al* teach the following compound  (Page 61, Example 18). Accordingly, *Bao et al* teach a structurally related compound which differs from the instant compound in two ways: FIRST, the phenyl in Example 18 (taught by *Bao et al*) is substituted with -OCH_3 whereas the phenyl in the instant compound is substituted with chloro; and SECOND, the other phenyl in Example 18 (taught by *Bao et al*) is pyridine in the instant compound. **Both** of the modifications to the compound taught by Example 18 in *Bao et al* would have been *prima facie* obvious for the following reasons:

10. As taught by *Williams et al* "[w]hen a lead compound is first discovered for a particular disease state, it often lacks the required potency and pharmacokinetic properties suitable for making it a viable clinical candidate… The medicinal chemist therefore must modify the compound to reduce or eliminate these undesirable features without losing the desired biological activity. Replacement or modification of functional groups with other groups having similar properties is known as isosteric or bioisosteric replacement" (Page 59). Although it is clear that "the use of bioisosteric replacement (classical or nonclassical) in drug development is highly dependent upon the biological system being investigated" and that "[n]o hard and fast rules exist to determine what bioisosteric replacement is going to work with a given molecule" it is also clear that "some generalizations have been possible" (Page 60). Notably, as taught by *Patani et*

al, one such generalization is that -OCH_3 and -Cl can replace each other (Page 3154, Figure 18), a modification that was associated with a decrease in compound half-life. Furthermore, as taught by *Williams et al*, another such generalization is that -CH= and –N= (which are classic biosteric groups) can replace each other (Page 61, Table 2.9). Indeed, *Patani et al* similarly teach that benzene and pyridine are classic ring equivalent bioisosteres (Page 3158, Column 1). Accordingly, in view of *Williams et al* and *Patani et al* it would have been *prima facie* obvious to modify the compound taught by *Bao et al* (Example 18) by replacing the methoxy group with a chloro group. Specifically, the skilled artisan would have been motivated to replace -OCH_3 with -Cl in order to optimize the pharmacokinetic properties of the compound in view of *Williams et al* and *Patani et al* with a reasonable expectation of success. Additionally, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to replace the –CH= group in benzene (as taught by *Bao et al*) with –NH= to form pyridine (as recited by the instant claims). The person of ordinary skill in the art at the time the invention was made would have been motivated to make the bioisosteric modification to synthesize similar compounds that retain biological activity, but have improved physiochemical properties and better pharmacokinetic behavior. Accordingly, instant claims 1-4, 10-14 and 18-19 are rejected as *prima facie* obvious.

11. Applicants traverse on the grounds that "there is no indication from *Bao et al* that Example 18, as opposed to the other examples, would clearly be the starting reference point from which a skilled artisan might identify a problem and pursue potential solutions" (Applicant Argument, Page 16). As stated in MPEP 2144.08 "a genus may be so small that, when considered in light of the totality of circumstances, it would anticipate the claimed species or

subgenus." Significantly, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic chemical formula inherently anticipated a claimed species within the genus because "one skilled in [the] art would… envisage *each member*" of the genus. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962, emphasis in original). Thus it is significant that *Bao et al* disclose only 20 examples. Accordingly, in the instant case, the skilled artisan would have been able to immediately envisage modifying any one of the 20 compounds (including Example 18) embodied by *Bao et al* according to *Williams et al* and *Patani et al*. As such, Applicants' argument is not found persuasive.

12. Applicant further traverses on the grounds that *Williams et al* and *Patani et al* - which are general medicinal chemistry texts - do not disclose compounds (such as the instant compounds) having activity as GlyT or potassium channel inhibitors. As such, Applicants contend that "[o]ne skilled in the art with knowledge of *Bao* would in no way be looking to *Williams* [or Patani] for specific teachings to modify compounds active against these targets" (Applicant Argument, Page 17). Applicants' argument is not found persuasive. Although Applicant is correct that neither *Williams et al* nor *Patani et al* are directed to GlyT or potassium channel inhibitors specifically, the skilled artisan would understand that *Williams et al* and *Patani et al* teach bioisosteric modifications which are applicable to compounds in general and which have been shown to predictably result in compounds having similar biological activity relative to the parent compound but distinct pharmacokinetic profiles. Since the compounds taught by *Bao et al* are "potassium channel inhibitors" (Title), the skilled artisan would have predicted that the well known bioisosteric modifications taught by *Williams et al* and *Patani et al* – when applied to the

potassium channel inhibitors taught by *Bao et al* – would provide compounds having similar activity as potassium channel inhibitors, but with distinct pharmacokinetic profiles. Thus, the skilled artisan would have made the above discussed modifications in order to synthesize similar compounds that retain biological activity, but have improved physiochemical properties and better pharmacokinetic behavior.

13. Additionally, via Declaration, Scott Wolkenberg identifies seven compound species, some of which demonstrate time dependent inhibition of CYP and some of which do not. Significantly, nothing is concluded by Mr. Wolkenberg in the Declaration. However, based on the Declaration, Applicants argue that "three out of the four 4-phenylpiperidine compounds were TDI+ while three out of three 4-pyridylpiperdine [sic] compounds were TDI-. This result clearly demonstrates an unexpected superior preclinical profile for the 4-pyridylpiperidine series over the 4-phenylpiperidine series" (Applicant Argument, Pages 17-18). However, this argument is not found persuasive since, in each instance, multiple modifications were made to the compared compounds. Thus, it is unclear whether the observed differences in activity were due to the replacement of phenyl with pyridine, as asserted by Applicants, or due to the other modifications.

14. Applicants also assert that "all the examples described in *Bao* have a methoxy group substituted on the benzamide portion, thus teaching away from the claims as presently amended" (Applicant Argument, Page 17). However, a disclosure that "does not criticize, discredit, or otherwise discourage the solution claimed" does not constitute a teaching away. In re Fulton, 391 F.3d 1195 (Fed. Cir. 2004). As such, it is not found persuasive that *Bao et al* teach away from the well known bioisosteres $-OCH_3$ and -Cl.

15. Instant claim 23 is drawn to a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of claim 1 or salt thereof. *Bao et al* specifically disclose that "[a]lso within the scope of this invention are pharmaceutical formulations comprising a compound of Formula I and a pharmaceutical carrier" (Page 9, Lines 13-15). Accordingly, claim 23 is rejected as *prima facie* obvious.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

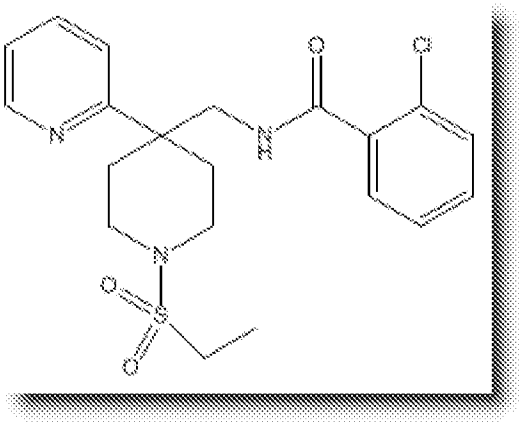
with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. **Claims 1-8, 10-14, 18-19 and 22-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4 and 18 of copending Application No. 10/579,261 in view of *Williams et al* (cited in a previous Action) and *Patani et al* (cited in a previous Action)**.

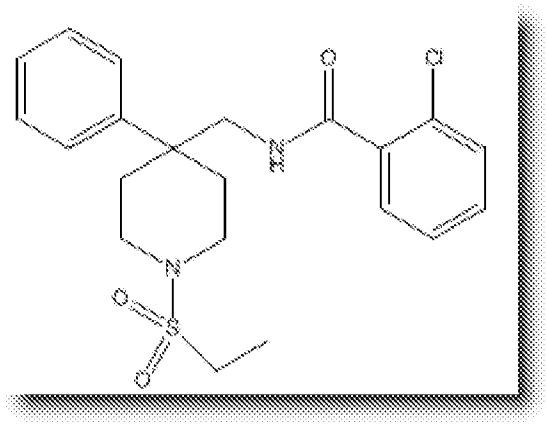
This is a provisional obviousness-type double patenting rejection.

18. As discussed above, instant claim 1 is drawn to a compound of formula (I) which encompasses the following hypothetical compound



wherein R^1 is hydrogen; R^2 is phenyl, which is substituted with R^{2a} and R^{2a} is halogen; R^3 is CH_2-CH_3; R^4, R^5 and R^6 are hydrogen; W, X, Y and Z are C; and m is zero, and which reads on claims 1-4, 10-14 and 18-19.

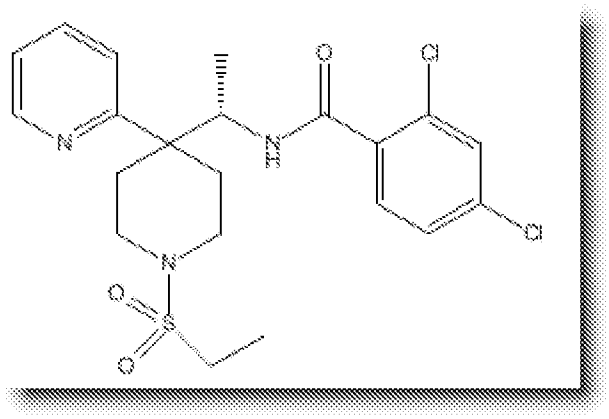
19. Claim 1 of the '261 application is drawn to a compound of formula (I) which encompasses the following hypothetical compound



wherein R^1 is hydrogen; R^2 is phenyl, which is substituted with halogen; R^3 is CH_2-CH_3; and R^4 and R^5 are hydrogen. Accordingly, the '261 application teaches structurally and functionally related compounds differing only in the substitution of benzene (as taught by the '261 application) with pyridine as recited by the instant claims.

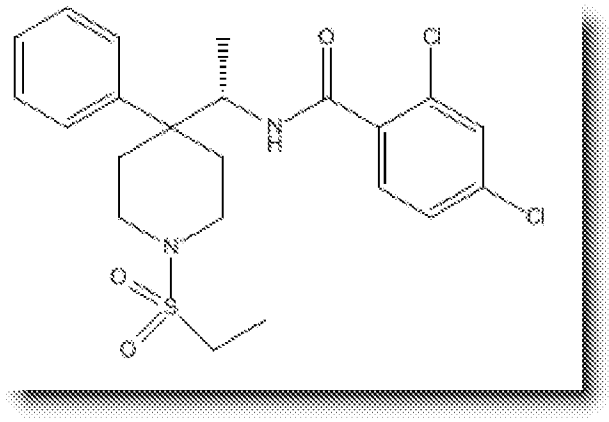
20. As discussed above, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to replace benzene in the compounds taught the '261 application with pyridine as claimed in the instant application in view of *Williams et al* and *Patani et al*. The person of ordinary skill in the art at the time the invention was made would have been motivated to make the obvious bioisosteric modifications to synthesize similar compounds that retain biological activity, but have improved physiochemical properties and better pharmacokinetic behavior.

21. Instant claim 1 also encompasses Applicant's elected specie; namely



which reads on claims 1-8, 11-14, 18-19 and 22.

22. Claim 4 of the '261 application is drawn to a compound of formula (Ib) which encompasses the following hypothetical compound



wherein R^2 is phenyl, which is substituted with one or more halogens; and R^3 is CH_2-CH_3. Notably, the only difference between the instant elected compound specie and the above compound encompassed by claim 4 of the '261 application is the substitution of benzene (as taught by the '261 application) with pyridine as recited by the instant claims. Accordingly, for all of the reasons discussed above, claims 1-8, 11-14, 18-19 and 22 (which are drawn to the instantly elected compound specie) are rejected.

23. Instant claim 23 is drawn to a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of claim 1 or salt thereof. Claim 18 of the '261 application recites a pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

Conclusion

The new ground(s) of rejection presented in this Office action are necessitated by Applicants' amendments to the claims. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614